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10/553,757

01/03/2007

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EXAMINER

CHANDRAKUMAR, NIZAL S

ART UNIT

PAPER NUMBER

1625

MAIL DATE

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09/01/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/553,757	<b>Applicant(s)</b> KVITNITSKY ET AL.	
	<b>Examiner</b> NIZAL S. CHANDRAKUMAR	<b>Art Unit</b> 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 23 March 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-5 and 7-31 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5, 7-31 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

This office action is responsive to Applicants Remarks filed 03/23/2009.

This is a non-final rejection.

#### **Response to Applicants arguments:**

##### ***Election/Restrictions***

Upon further consideration, the previously presented restriction requirement is withdrawn with respect to claims 15-31.

Applicant elected, see papers filed 09/22/2009

Group 1, claim(s) 1-14, drawn to compounds and composition containing compounds of formula (I) wherein R3 and R4 are independently H.

for prosecution.

Claims 1-5, 7-31 are pending and are examined to the extent that they read on the elected subject matter.

**Objection:** Claims 1-5, 7-9 are objected to for containing non-elected subject matter.

##### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Upon further consideration previously presented rejection of claims 1-5, 7-14 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement

Art Unit: 1625

requirement is recast as scope of enablement and is presented later in this office action following response to applicants remarks.

Applicant's arguments are based on:

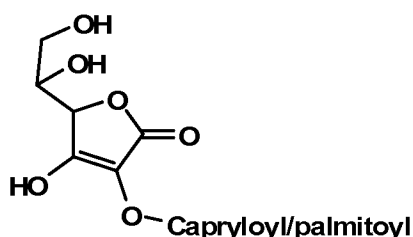
1. the enablement rejection is inconsistent with concurrent obviousness rejection
2. the office's position on the 'makeability' of the claimed compounds is incredible because of the two examples of synthesis with the additional details in pages 16-20.

Response:

1. It is the Examiner's position that the previously presented rejection is not an 'improper squeeze', because the rejection ultimately relates to possession issue. However, the rejection as previously presented is withdrawn. See below.

2. The office's position on the .makeability of the claimed compounds is not incredible, because

the product of step 4 in the above-mentioned two Examples in the specification provides for the preparation of



and, does not provide for making the sodium salt of the above as the title of step 4 implies. That is, step 4 does not lead to salts (R2 claim limitations) but is enabling for making compounds wherein R2 is H.

One skilled in the art would anticipate the process of step 4 to provide compounds of instant formula wherein R2 is H, not any of the R2 possibilities listed in

Art Unit: 1625

the claims. It is well known in the art that the contact of a salt (in this case sodium salt from step 3) with acid is anticipated to provide an acid, i.e., the protonated form of the (instantly claimed) salt.

The applicant did not have possession of the compounds of the elected group 1. Applicants pointed out citations in pages 1-6 of the specification were fully considered in the context of the instant claim limitations. Compare Example 1 in page of Shimizu et al. EP 0 619 313 A1 with the above-mentioned instantly disclosed steps 4.

With respect to R3 and R4:

There is no direction, guidance or working example in the specification for making compounds wherein R3 and R4 are independently H. As stated in the previous office action, there is no enabling disclosure for making compounds wherein one of the hydroxyls corresponding to R3 and R4 is selectively derivatized. Methods for selective protection/deprotection strategies for similar, multiple OH functionalities in proximity is not taught by teachings in the specification or by citations to prior art. This part of the rejection could be overcome by amending the claims to recite --R3 and R4 are both hydrogens--. For this reason, as previously indicated, the obviousness rejection is not inconsistent with enablement rejection when the claims are drawn to compounds wherein R3 and R4 are both hydrogens.

That is, teachings in the present in the specification in the context of what was known in the prior art was taken into consideration and the rejection is based on consideration of **all** the Wands factors (MPEP 2164.01 (a)). Shimizu and Strelchler

Art Unit: 1625

references were cited not in the anticipatory sense. One skilled in the art would anticipate making salts of ascorbic acid is analogous to making salts of beta-ketoesters, since ascorbic acid is a beta-ketoester, the lactone being a cyclic ester rendering the R2 = H an acidic hydrogen that could be deprotonated using base. However, in the context of the claim limitations for the additional functions in the claimed formula coupled with the details of the above-disclosed step 4, the instant specification is lacking methods for making salts (R2 limitations). As indicated by the applicant, (page 4, line 1 of paper filed 03/23/2009), the 'additional guidance' needed; which is not disclosed in the specification. The 'additional guidance' (see page 4, line 1 of applicant paper filed 03/23/2009), acknowledged as needed to make the instant compounds is not found in the specification.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Previously presented rejection of claims 1-5, 7-14 under 35 U.S.C 103 over the teachings of Shimizu et al. and Strelchler et al. is maintained for reasons of record.

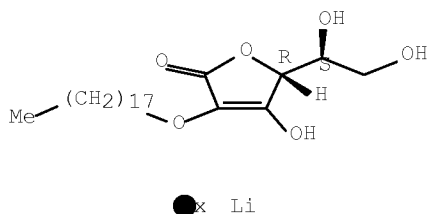
Applicant's arguments were fully considered but are not persuasive.

Applicants state that to come up with applicants compounds from the Shimizu et al teaching is like 'figuring out the combination of a safe from looking at the dial, i.e.,

Art Unit: 1625

everything is there but how to put it all together in the right combination is next to impossible' This is not persuasive. The instant claims are also drawn to large of number of structural possibilities similar to the generic disclosure of Shimizu et al.

As discussed previously Shimizu et al. teach



Applicant's claims are drawn to compounds corresponding to the above Li salt wherein Li is replaced with other counter ions (R2 limitations). The above formula corresponds to R1 C18 alkyl, when the instant claim limitation calls for R1 C17 alkyl. Adjacent homologs are obvious variants of each other.

With regards to Strelchler's teachings applicant state that the situation is similar to that of Shimizu et al. Further, applicant state that the variable at the 2-position of the formulae of the prior art and instant claims are different such that applicants compounds do not fall within the generic disclosure of Strelchler's formula. This is not persuasive. Strelchler's '906 is not an anticipatory reference. However, claim 1 of '906 states the various possibilities for R2, R3 and R4. The acyl possibility in '906 compounds, corresponding to instant R1, has double bonds in the acyl chain (sorbic acid chain) while the instant R1 groups do not specifically claim such acyl groups with double bonds except in claim 5.

Art Unit: 1625

**New Rejection:**

The following rejection is presented in view of withdrawal of restriction requirement and in view of recasting of the previously presented 112-1 rejection.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-14 (and dependent claims 15-31 by virtue of dependency, see below) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the some of intermediates to make the instantly claimed compounds, does not reasonably provide enablement for making the specific salts (R2 claim limitations) of the instant claims. Thus the specification provides for making compounds wherein, R3, R4 and R2 all are hydrogens. Claims 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling (based on prior art teaching) for some of the use of compositions containing ascorbic acids , does not reasonably provide enablement for the use of the compositions in treatment of all forms of cancer and immune system. The specification sates that **the** ascorbic acid derivatives are expected to show effectiveness comparable to that of L-ascorbic acid or better, on collagen synthesis. It is not seen where in the specification enabling disclosure with respect to the use of **the** ascorbic acid derivatives in compositions for the treatment of generically claimed cancer or for the enhancement of



Art Unit: 1625

immune system in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make and use** the invention commensurate in scope with these claims.

. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art.

All of the factors have been considered with regard to the claims, with the most relevant factors discussed below:

Lack of enablement with respect to variable R3 and R4:

The claims are drawn to variables R3 and R4 that are independently H. The specification discloses compounds in which R3 and R4 are either simultaneously protected as isopropylidene ketal or R3 and R4 are both simultaneously H. This is consistent with the prior art teachings See rejection under 103. There is no guidance, direction or working example for making compounds wherein R3 is H and R4 is anything other than H. There is no enabling disclosure for selectively making compounds wherein one of the hydroxyls corresponding to R3 and R4 is selectively

Art Unit: 1625

derivatized. Step 4 in the example removes the ketal linkage resulting in the formation of compound in which R3 and R4 are both hydrogens. Methods for selective protection/deprotection strategies for similar, multiple OH functionalities in proximity is not taught by teachings in the specification. The specification does not disclose any prior art citation in lieu of enabling disclosure for obtaining such compounds.

Lack of enablement with respect to variable R2:

The claims are drawn to compounds of formula I wherein R2 is ammonium or a metal cation. Step 4 of working Examples 1 and 2 allegedly describe the synthesis of sodium salt of 2-caryloyl and 2-plamitoyl ascorbic acid starting from the product of the step 3 which describes the basification of 5,6-isopropylidene ascorbic acid with sodium carbonate thus enabling the formation of R2 sodium cation, that is compound of formula I wherein R3 and R4 are protected as isopropylidene ketal. The described reaction in step 4 involves treatment of the product of step 3 with methanolic aqueous HCl and washing with sodium chloride up to pH7. The treatment of an isopropylidene compound with aqueous HCl acid is known in the art to deprotect the hydroxy groups leading to the formation of R3 and R4 H. However, acid treatment of the sodium salt (R2=Na) of an organic acid is expected to result in the neutralization of the salt resulting in the formation of R2 = H. Even though the specification discloses that the product is washed with sodium chloride to pH 7, it is art recognized fact that washing of organic acids (R2 =H) with sodium chloride can not lead to salt formation. The specification does not provide any analytical data that would support the formation of sodium salt in step 4.

Use aspect of the enablement requirement:

Art Unit: 1625

The dermatological use of ascorbic acid derivatives is well documented. With respect to allegedly patentably distinct instant compounds, for use aspect of 112 requirement the disclosure is limited and is in the form of the last sentence of Example 3 (page 17) of the specification. Claims 16-18 are drawn to treatment of cancer and enhancement of immune system.

Based on prior art teachings the use of ascorbic acid compounds in cosmetic, dermatological and neutraceutical applications as well as in the treatment of cutaneous cancer and photo damaged skin can be acknowledged. However it is not seen where in the specification enabling disclosure is found for use of instant compositions in the treatment of all types of cancer and for the treatment of immune system in general. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The following eight different factors (see *Ex parte Foreman*, 230 USPQ at 547; *Wands, In re*, 858.F. 2d 731, 8 USPQ 2d 1400, Fed. Cir. 1988) must be considered in order for the specification to be enabling for what is being claimed: Quantity of experimentation necessary, the amount of direction or guidance provided, presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability and the breadth of claims. In the instant case, the specification is not enabling based on at least four of the above mentioned eight different factors such as quantity of experimentation necessary, the amount of direction

Art Unit: 1625

or guidance provided, presence of working examples, state of the prior art, unpredictability and the breadth of claims.

There is no working example present showing efficacy of instant compounds in known animal models of tumor regression. The instant compounds of formula I encompasses hundreds of thousands of compounds based on the R variables wherein these substituents are layered on top of other substituents and therefore, in absence of such teachings, guidance, presence of working examples, unpredictability and prior art, it would require undue experimentation to demonstrate efficacy of instant compounds in every known cancer in the art and hence their utility for treating and/or preventing these disorders.

It is well known in the art that there are multiple mechanisms involved in the etiology of hyperproliferative cancer disorders. Therefore, correcting only one of these several mechanisms will not completely cure or prevent that specific disease condition. Hyperproliferative is just an umbrella term. Cancer is not a single disease. It is a large and complex family of malignancies that can affect virtually every organ in the body. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed Simone

Art Unit: 1625

article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

The Cancer Handbook, provides that: "Analysis of patient's enzyme systems or genes for drug metabolism and detoxification as well as tumor-specific factors such as the presence or absence of multiple drug-resistant genes may lead to improvements in selection of active drugs, their dosage and timing of therapy. However, the molecular foundations for determination of a tumor's resistance or sensitivity to specific chemotherapies is still not yet understood on either an empirical or a scientific basis and unfortunately there are still few, if any, applications in routine cancer care."

For similar reasoning, the specification is not enabling for enhancement of immune systems as claimed.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See *Ex parte Jovanovics*, 211 USPQ 907, 909; *In re Langer* 183 USPQ 288. Also note *Hoffman v. Klaus* 9 USPQ 2d 1657 and *Ex parte Powers* 220 USPQ 925 regarding type of testing needed to support *in vivo* uses.

Applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'.

Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved".

Art Unit: 1625

See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIZAL S. CHANDRAKUMAR whose telephone number is (571)272-6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1625

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/Nizal S Chandrakumar/  
Examiner, Art Unit 1625